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Spierenburg, G.; Grimison, P.; Chevreau, C.; Stacchiotti, S.; Piperno-Neumann, S.; Cesne, A. le; ... ; Gelderblom, H.

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Original Research

Long-term follow-up of nilotinib in patients with advanced tenosynovial giant cell tumours Long-term follow-up of nilotinib in TGCT

Geert Spierenburg [a,*], Peter Grimison [b], Christine Chevreau [c], Silvia Stacchiotti [d], Sophie Piperno-Neumann [e], Axel Le Cesne [f], Virginia Ferraresi [g], Antoine Italiano [h], Florence Duffaud [i], Nicolas Penel [j], Severine Metzger [k], Sylvie Chabaud [k], Lizz van der Heijden [a], David Pérol [k], Michiel A.J. van de Sande [a], Jean-Yves Blay [l], Hans Gelderblom [m]

[a] *Department of Orthopedic Surgery, Leiden University Medical Center, Leiden, Netherlands*
[b] *Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, Australia*
[c] *Department of Medical Oncology, Institut Claudius Regaud, Institut Universitaire Du Cander de Toulouse, Toulouse, France*
[d] *Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*
[e] *Department of Medical Oncology, Institut Curie, Paris Sciences et Lettres Research University, Paris, France*
[f] *Department of Cancer Medicine, Gustave Roussy, Villejuif, France*
[g] *Sarcomas and Rare Tumors Departmental Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy*
[h] *Department of Medical Oncology, Institut Bergonié, Bordeaux, France*
[i] *Department of Medical Oncology, Hôpital de La Timone, Aix-Marseille Université, Marseille, France*
[j] *Department of Medical Oncology, Center Oscar Lambret, Lille University Lille, France*
[k] *Department of Clinical Research and Innovation, Léon Bérard Cancer Center, Lyon, France*
[l] *Department of Medical Oncology, Center Léon Bérard Cancer Center, Lyon, France*
[m] *Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands*

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KEYWORDS
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Abstract ***Background:*** Diffuse-type tenosynovial giant cell tumour (D-TGCT) is a non-malignant but locally aggressive tumour driven by overexpression of colony-stimulating factor-1 (CSF1). CSF1R inhibitors are potential therapeutic strategies for patients not amenable to surgery. We report here the long-term outcome of nilotinib in patients with advanced

Abbreviations: TGCT, Tenosynovial giant cell tumour; PVNS, Pigmented villonodular synovitis; CSF, Colony-stimulating factor; CSF1R, Colony-stimulating factor 1 receptor.

* *Corresponding author:* Department of Orthopedic Surgery Leiden University Medical Center Postzone J11-R-70 PO Box 9600 2300 RC Leiden, Netherlands.
E-mail address: G.Spierenburg@lumc.nl (G. Spierenburg).

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CSF1;
CSF1R inhibitor;
Tyrosine kinase inhibitor

D-TGCT treated within a phase II prospective international study (ClinicalTrials.gov: NCT01261429).

Methods: Patients were enrolled between December 2010–September 2012 at 11 cancer centres. Eligible patients had histologically confirmed D-TGCT, not amenable to surgery. Patients received nilotinib until evidence of progression, toxicity or a maximum of one year. Long-term data were retrospectively collected after the completion of the phase II trial. Patients with nilotinib treatment ≥12 weeks and follow-up ≥12 months were included for long-term analysis.

Results: Forty-eight of 56 enrolled patients were included. Median treatment duration was 11 months; 31 (65%) patients completed the treatment protocol. After 102 months of follow-up (median; range 12–129), 25 patients (52%) had progression. The median progression-free survival (PFS) was 77 months. The five-year PFS rate was 53%. Fifteen patients (n = 15/46; 33%) experienced clinical worsening after 11 months (median). Twenty-seven patients (58%) received additional treatment, after which eleven patients (n = 11/27; 41%) had a second relapse. Nine patients required a subsequent treatment, primarily other CSF1R inhibitors (n = 6/9; 67%). No unfavourable long-term effects were observed.

Conclusion: This long-term analysis of nilotinib for advanced D-TGCT showed that about half of the patients had progression and underwent additional treatment after 8.5 years follow-up. Contrarily, several patients had ongoing disease control after limited treatment duration, demonstrating the mixed effect of nilotinib.

1. Introduction

Tenosynovial giant cell tumour (TGCT) is a rare, connective tissue tumour affecting the synovium of joints, bursae and tendon sheaths in a relatively young population [1,2]. TGCT consists of two main subtypes: localized-type (L-TGCT) and diffuse-type (D-TGCT), of which the diffuse variant can behave locally aggressive [3]. Formerly the names giant cell tumour of tendon sheath and pigmented villonodular synovitis (PVNS) were used for these subtypes, respectively. Malignant TGCT is considered as the third subtype; however, this is extremely rare [4].

TGCT is predominantly driven by chromosomal aberrations involving *colony-stimulating factor 1* (*CSF1*) gene, leading to an overexpression of CSF1 [5–7]. CSF1 overexpression stimulates the growth and proliferation of neoplastic tumour cells and also accumulates cells of the macrophage lineage expressing CSF1 receptor (CSF1R) [6]. There is no clear histological distinction between the two TGCT subtypes; they are predominantly distinguished by radiological and clinical presentation [8].

Complete surgical excision is the mainstay of treatment for TGCT, curing L-TGCT in 80–90% [9–11]. For D-TGCT, complete resection is often not achievable or associated with morbid surgery due to the extensive villous tumour growth intra- and extra-articular [12,13]. Local relapses occur in more than 50%, and repeated surgery is usually necessitated [13]. Both repeated surgery and mutilating surgery in advanced cases of TGCT can cause iatrogenic morbidity. For these cases, there is an unmet medical need for additional therapeutic strategies. Radiotherapy can be used as (neo)adjuvant treatment or stand-alone, but data regarding the efficacy of radiotherapy is limited and of low-level quality [14,15]. Additionally, radiotherapy is related to complications such as avascular necrosis, osteoarthritis and even radiation-induced malignancies, an important issue for a locally aggressive yet benign disease [14,16–18].

More recently, novel drugs targeting CSF1R are being developed and the safety and efficacy are evaluated for patients with relapsing or inoperable D-TGCT [19–24]. CSF1R-inhibiting drugs, consisting of CSF1R antibodies and tyrosine kinase inhibitors (TKI), have shown substantial clinical activity [25]. A phase II clinical trial evaluating the effect of nilotinib in patients with locally advanced D-TGCT, was started in 2010 (ClinicalTrials.gov: NCT01261429) [23]. Nilotinib is a phenylaminopyrimidine, inhibiting several tyrosine kinases, including ABL, KIT, platelet-derived growth factor receptors and CSF1R. Nilotinib is an approved drug for chronic myelogenous leukaemia [26]. Nilotinib was found to have short-term anti-tumour activity, achieving disease control in more than 90% of patients with advanced D-TGCT [23].

The effect of CSF1R antagonists on TGCT has only been studied in the last decade. Therefore, data regarding their long-term efficacy is limited. Nevertheless, it is essential to know the long-term effects of CSF1R inhibitors because TGCT has its onset in a relatively young patient population. The present study is an extension of the previously published phase II clinical trial and the article reports the long-term outcomes of nilotinib in patients with advanced inoperable or relapsing D-TGCT [23].

2. Methods

This study describes the long-term effect of nilotinib in patients with locally advanced D-TGCT. This is a long-term report of a multi-centre, open-label, single-arm, phase II trial, registered with ClinicalTrials.gov, number NCT01261429 [23,27]. Patients were enrolled at 11 cancer centres or hospitals in four countries (France, the Netherlands, Italy and Australia) between December 2010 and September 2012. A summary of this study and a comprehensive overview of the in- and exclusion criteria can be found in the appendix (supplementary Table 1). The study protocol of the phase II trial was approved by the local ethics committee at each site and is available online [23,27]. This study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

2.1. Procedures

During the phase II trial, patients received oral nilotinib 400 mg twice per day until disease progression, intolerable toxicities, patient's decision to withdraw or completion of one-year treatment. Patients were followed up at fixed time points up to 12 months. Patients who were progression-free after one year of treatment could receive continuation of nilotinib as compassionate treatment. Radiological response was assessed by CT scan or MRI according to Response Evaluation Criteria in Solid Tumors 1.1. After one year of treatment, local teams classified tumours as operable or not operable.

As the study did not foresee a follow-up period after the end of the first year, the long-term effect of nilotinib was studied by retrospectively updating the investigator-assessed progression in October 2021. This long-term follow-up was performed at each site according to the local schedule. Data regarding progression following nilotinib treatment and subsequent therapies were retrospectively collected from patient medical records. This study primarily focused on patients receiving at least 12 weeks of nilotinib treatment (the primary endpoint in the phase II trial) and a follow-up of ≤12 months for long-term analysis.

2.2. Outcomes

The primary endpoint was the long-term progression-free survival (PFS). Secondary endpoints were duration of response, median time to progression, clinical worsening, nilotinib-related long-term adverse events, operability after nilotinib and types of subsequent therapies.

2.3. Statistical analysis

Continuous data were described using means and standard deviations (SD) or medians and interquartile ranges (IQR). Kaplan–Meier method was used to analyse PFS. The statistical analyses were performed in IBM Statistical Package for Social Statistics (SPSS) 25 (Chicago, IL, USA) was used for analysis. A swimmer plot was created using RStudio version 4.1.0 (RStudio Team, Boston, United States).

3. Results

During the phase II trial, 56 patients were enrolled. Data from all included patients were made available by the investigators from the recruiting institutions. Six patients (10.7%) discontinued treatment before the primary endpoint at 12 weeks and two patients (3.6%) had a follow-up ≤12 months and were not included in the long-term analysis. A total of 48 of 56 patients (85.7%) were included in this long-term analysis (Fig. 1). Two of the eight patients not included for long-term analysis had progressive disease as the best objective response within 12 weeks of treatment. Of the 56 patients enrolled during the phase II trial, 29 patients (51.8%) had tumour progression and the median PFS was 77 (IQR 12.0–97.0) months.

The 48 patients included for the long-term analysis had a mean age of 37 years (SD ± 13.7) at nilotinib initiation. Before nilotinib initiation, three patients (6.3%) received imatinib, two patients (4.2%) had radiotherapy and 32 patients (66.7%) underwent surgery with a median of 24 months (IQR 11.0–50.0) before initiation with nilotinib. Table 1 presents the patient characteristics of the included patients.

For the 48 patients, median duration of nilotinib treatment was 11 months (IQR 8.0–12.0) and 31 patients (52.1%) completed 12 months of treatment according to the protocol (Table 1). Six patients continued nilotinib as a compassionate treatment after one year for 5–48 additional weeks (total treatment duration range 13–22 months). Seventeen patients (35.4%) discontinued treatment prematurely, primarily due to patients' refusal (n = 5), disease progression (n = 4), tumour resection (n = 4), toxicity (n = 2). Median time to treatment failure was seven months (IQR 4.5–8.5). Under nilotinib treatment, three patients (6.3%) achieved a partial response as best overall response and 45 patients (93.8%) achieved stabilization of disease. The four patients with on-treatment progression achieved stable disease as best overall response before progression, and then progressed 5–8 months after starting with nilotinib treatment.

3.1. Long-term follow-up of TGCT

The median follow-up since nilotinib initiation was 102 months (8.5 years; IQR 65.0–111.8 months) (Table 2). Tumour progression was reported in 25 of 48 patients (52.1%), in 18 cases (72.0%) after nilotinib completion of which four patients received a subsequent treatment

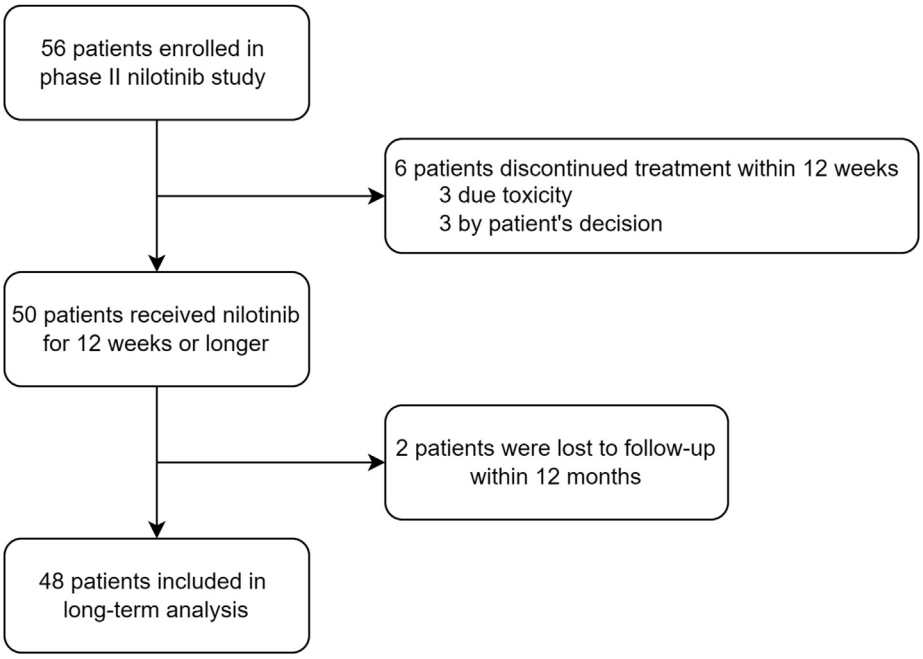


Fig. 1. Flowchart of patients included for the long-term analysis.

before progression. The three patients who achieved a partial response remained without tumour progression and their duration of response till the last moment of follow-up were 49, 63 and 110 months, respectively. Amongst the 25 patients who progressed, the median time until progression was 16 months (IQR 8.0–41.5). The median PFS was reached after 77 months (Fig. 2). PFS rates at three, five and seven years were 62.0% (SD ± 13.9), 52.7% (SD ± 14.5) and 49.7% (SD ± 14.7), respectively (Fig. 2). Nine of eleven patients (82%) who received nilotinib for approximately one year (11–12 months) and did not undergo a subsequent treatment remained progression-free after a median of 79 months. Furthermore, the five-year PFS rate from treatment discontinuation for patients completing treatment protocol and who did not have progression or clinically deteriorate under nilotinib was 71.5% (SD ± 19.4) (Fig. 3). Fifteen patients (n = 15/46, for two patients this data was not available; 32.6%) experienced clinical worsening after a median of eleven months (n = 14; IQR 7.0–30.5) of which in seven cases (46.7%) under nilotinib treatment. No long-term adverse events were reported.

3.2. Subsequent therapies

D-TGCT was assessed as an operable tumour in 31 of 48 patients (64.6%) at the completion of the phase II trial (Table 2). Twenty-seven of 48 patients (58.3%) had subsequent therapy (median 6 months; IQR 2.0–18.0) after nilotinib cessation (Table 2). Patients mainly underwent synovectomies (n = 19/27; 70.4%) or received other CSF1R inhibitors (n = 6/27; 22.2%) as first subsequent treatment. Seventeen of the 31 patients (54.8%), who were assessed as operable (54.8%), underwent an additional synovectomy. In addition, nine of 23 patients (39.1%) having no tumour progression underwent a synovectomy following one-year nilotinib treatment. Six of 19 patients (31.6%) undergoing a synovectomy and 4 of 6 patients (66.7%) receiving another CSF1R inhibitor after nilotinib had tumour progression (Fig. 4). TGCT progressed after a median of 17 months (range 7.0–84.0) following a second CSF1R inhibitor. In total, 11 of 27 patients (40.7%) were not cured after a subsequent therapy and nine (81.8%) had an additional treatment after 21 months (median; IQR 5.5–61.5). The majority received other CSF1R inhibitors (n = 6/9; 66.7%). A more extensive overview of the individual patients' TGCT course and related treatments can be found in Fig. 5.

4. Discussion

The interest in CSF1R inhibitors for TGCT is growing, offering new therapeutic possibilities for patients not amenable to surgery [28]. TGCT has its onset in a relatively young patient population and is a non-malignant disease [2,3]. Therefore, patients will be followed for a long period, and it is of great importance to know the long-term effects of therapeutic strategies. This study evaluates the long-term efficacy of nilotinib in patients with progressive, advanced D-TGCT patients and, to our knowledge, contains the longest follow-up of TGCT treated with CSF1R inhibitors.

Nilotinib was the first TKI prospectively investigated in patients with advanced D-TGCT and provided a

Table 1
Baseline demographics and treatment characteristics.

Features	N = 48
Age, years, mean	36.6 (13.7)
Sex	
Women	24 (50.0)
Men	24 (50.0)
Time since diagnosis, months, median	22 (4.0–86.0)
Primary tumour location	
Knee	23 (47.9)
Hip	6 (12.5)
Ankle	7 (12.5)
Foot	5 (10.4)
Ulna	1 (2.1)
Wrist	2 (4.2)
Hand	3 (6.3)
TMJ	1 (2.1)
Previous treatment with imatinib	3 (6.3)
Time since imatinib start, months, median	13.3 (5.1)
Previous treatment with radiotherapy	2 (4.2)
Time since radiotherapy, months, mean	48.5 (16.3)
Previous surgery	32 (66.7)
Time since last surgery, months, median	24 (11.0–50.0)
Duration of treatment, months, median	11 (8.0–12.0)
Treatment duration of 12 months (according to protocol)	25 (52.1)
Treatment duration >12 months (compassionate use after end of protocol)	6 (12.5)
Treatment duration <12 months	17 (35.4)
Time till treatment discontinuation, months, median	7 (4.5–8.5)
Reason treatment discontinuation	
Patient's refusal	5 (29.4)
Disease progression	4 (23.5)
Tumour resection	4 (23.5)
Toxicity	2 (11.8)
Investigators choice	1 (14.3)
Other	1 (14.3)
Best OR	
Partial response	3 (6.3)
Stable disease	45 (93.8)

Data are n (%), mean (standard deviation) or median (interquartile range).
OR Overall response; *TMJ* Temporomandibular joint.

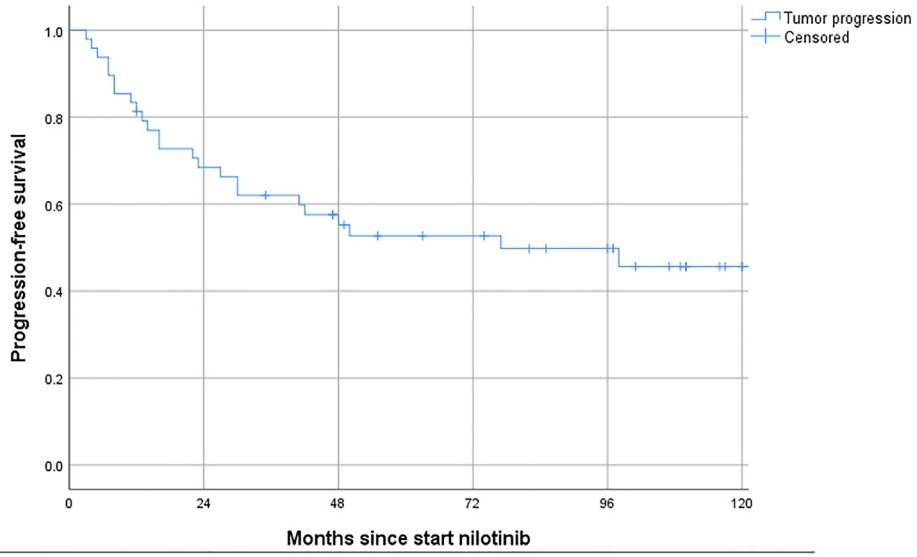
Table 2
Long-term follow-up characteristics.

Features	N = 48
Total follow-up, median, months	102 (65.0–111.8)
Progression disease	**25 (52.1)**
Time to tumour progression, months, median	16 (8.0–41.5)
Under nilotinib	7 (28.0)
After nilotinib	18 (72.0)
Clinical worsening*	**15 (32.6)**
Time to clinical worsening, months, median	11 (7.0–30.5)
Under nilotinib	7 (46.7)
After nilotinib	8 (53.3)
Operable tumour after start nilotinib	31 (64.6)
Underwent surgery	17 (54.8)
First subsequent treatment after nilotinib	**27 (56.3)**
Synovectomy	19 (70.4)
Other CSF1R inhibitors	
Imatinib	4 (14.8)
Emactuzumab	2 (7.4)
Other	
Total knee arthroplasty	1 (3.7)
Embolization	1 (3.7)
Time to subsequent therapy*, months, median	6 (2.0–18.0)
Progression after subsequent therapy	**11 (22.9)**
Time to progression from subsequent therapy,months, mean	27 (27.7)
Second subsequent treatment after nilotinib	**9 (18.8)**
Synovectomy	2 (22.2)
Radiotherapy	1 (11.1)
Other CSF1R inhibitors	
Imatinib	1 (11.1)
Emactuzumab	3 (33.3)
Pexidartinib	1 (11.1)
Vimseltinib	1 (11.1)
Time from first subsequent therapy to second subsequent therapy, months, median	21 (5.5–61.5)

Data are n (%), mean (standard deviation) or median (interquartile range).
* For two patients this data was missing.

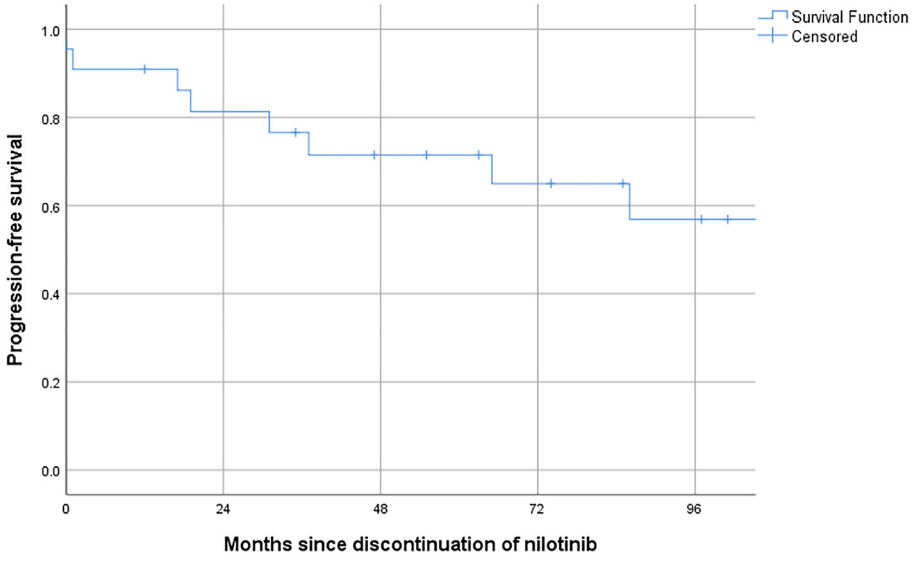
benchmark for alternative therapeutic strategies. As a result, a follow-up of more than eight years could be achieved to evaluate the long-term efficacy of nilotinib. Although most patients with progressive D-TGCT reached at least stabilization of disease under nilotinib and a considerable amount of patients remained progression-free after a brief treatment duration, radiological tumour progression and clinical worsening frequently occurred after a relatively short period. Higher PFS rates were observed for patients completing treatment protocol and showing clinical benefit. Contrarily, half of the patients had subsequent therapies, demonstrating the mixed efficacy of nilotinib. Subsequent therapies after nilotinib mainly consisted of synovectomies and other CSF1R inhibitors. The relapse rates were lower in patients treated by surgery following nilotinib than would be expected from postoperative relapse rates reported in literature [13,29]. Although we cannot conclude that nilotinib followed by surgery improves PFS based on this small heterogeneous group and the lack of a control group, multi-modality treatment including a CSF1R inhibitor and synovectomy deserves further exploration. The proportion of patients who received another CSF1R inhibitor as subsequent treatment was relatively high, considering that CSF1R inhibitors are only available as part of trials outside the US.

Since the first report of the activity of CSF1R inhibitors in TGCT, several drugs have been developed and investigated [28]. The long-term efficacy of several other TGCT-related drugs has been studied, comprising imatinib and pexidartinib (both TKIs) and emactuzumab (CSF1R antibody) reporting a median follow-up of 52 months, 39 months and 24 months, respectively [30–32]. Better overall responses were observed for these CSF1R inhibitors, although patients receiving imatinib or pexidartinib discontinued treatment more often. However, an external comparison cannot be made, since these drugs were investigated in different designs and cohorts. Currently, only pexidartinib is approved in the US by the



Years since nilotinib	0	2	4	6	8	10
Patients at risk	48	32	24	19	15	3

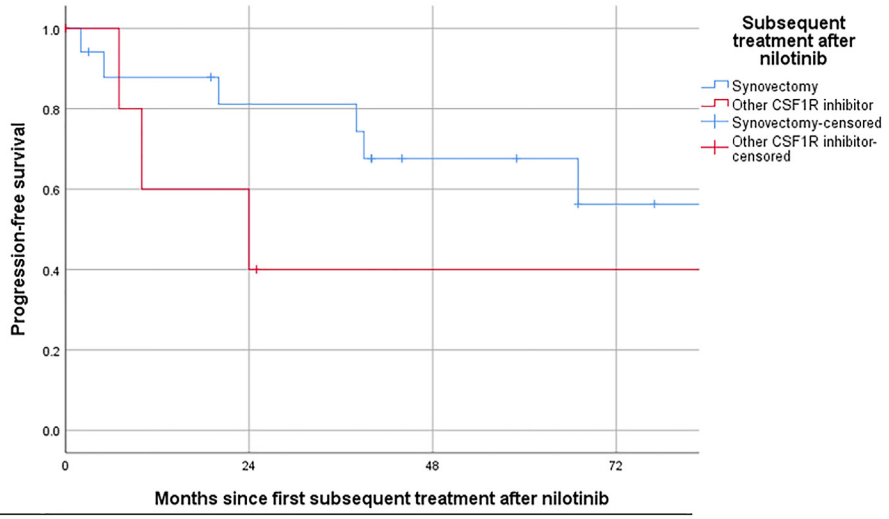
Fig. 2. Progression-free survival since start of nilotinib (Kaplan–Meier analysis).



Years since treatment discontinuation	0	2	4	6	8
Patients at risk	22	17	13	10	7

Fig. 3. Progression-free survival since discontinuation of nilotinib of patients completing treatment protocol and not having disease progression or clinical deterioration under nilotinib treatment (Kaplan–Meier analysis).

Food and Drug Administration [33]. The European Medicines Agency has not approved medical treatment for TGCT to date due to the safety profiles [34]. CSF1R inhibitors are associated with relatively high rates of adverse effects in relation to a young healthy population with, albeit cumbersome, benign disease. Nilotinib was assumed to have a more favourable tolerability profile than imatinib, causing less soft tissue and facial oedema [23,35]. During the phase II trial, 96% of the patients experienced treatment-related adverse events, of which six (11%) patients had at least one grade 3 treatment-related adverse events [23]. Fourteen (25%) patients discontinued treatment for reasons other than disease progression or an operable tumour, including toxicity, investigator's choice and patient's withdrawal. In other studies, investigating the safety and efficacy of CSFR1 inhibitors, even complications such as liver failure are reported [36]. In a non-life-threatening disease, it is essential to achieve a considerable benefit/risk ratio since patients are less willing to accept severe adverse effects.



Years since subsequent treatment	0	2	4	6
Patients at risk:				
Synovectomy	17	12	7	4
TKI	6	3	1	1

Fig. 4. Progression-free survival following the first subsequent treatment after nilotinib (Kaplan–Meier analysis).

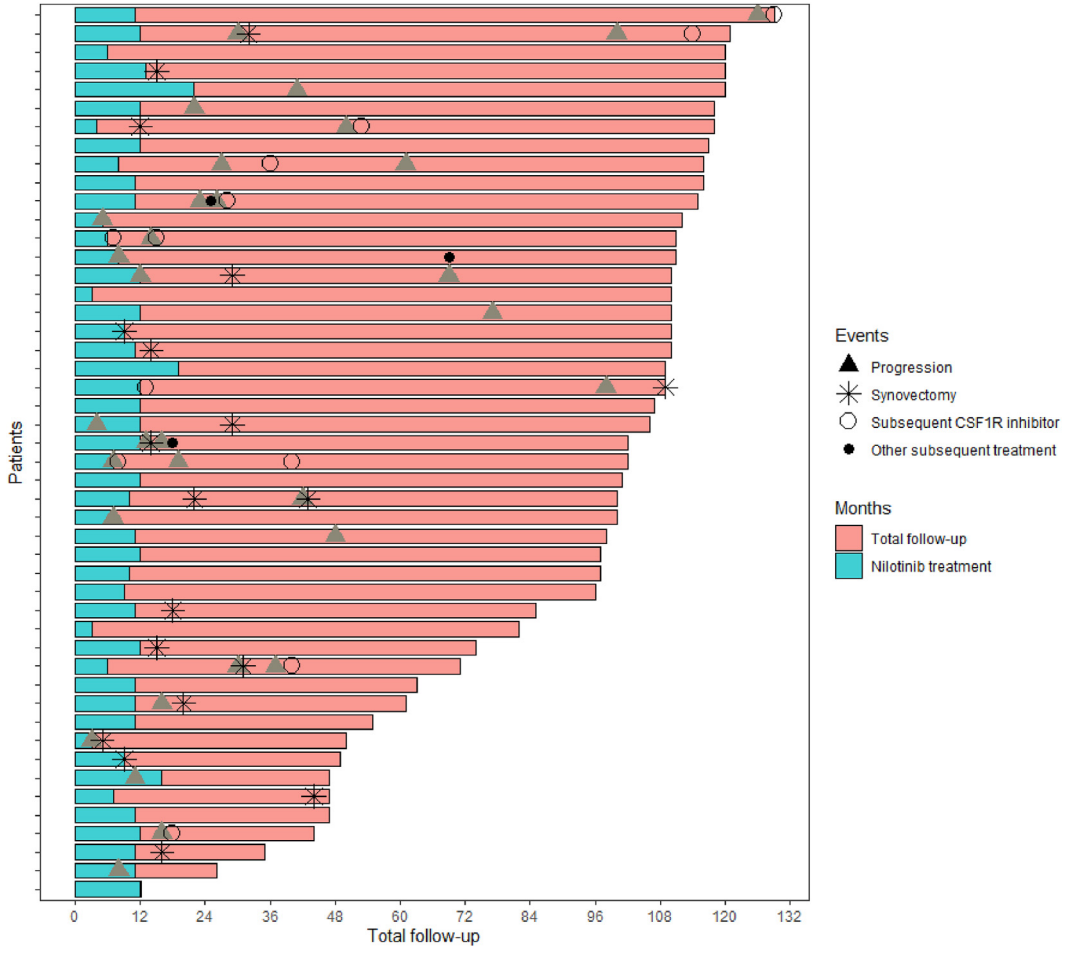


Fig. 5. Swimmer plot showing the duration of nilotinib treatment and follow-up in individual patients with locally advanced D-TGCT included for long-term analysis.

Especially, when complete response is not achieved and treatment could be chronic. Reassuringly, no long-term adverse events were observed during follow-up in this study. Nilotinib's patent expires in 2023 in both the United States and the European Union, and could be a possible solution as a low-cost off-label drug [37].

More recently, new CSF1R inhibitors have been developed and investigated, such as cabiralizumab and vimseltinib [22,38]. Apparently, cabaralizumab is not developed further whereas vimseltinib is currently being explored in a phase III registration study (MOTION) [39]. With the arrival of CSF1R inhibitors showing greater potential, the current role of nilotinib in TGCT treatment can be questioned. In addition to systemic therapies, the effect of intra-articular injections with CSF1R inhibitors is being studied, which are expected to cause less systemic adverse events but may be locally effective [40]. The first results are awaited.

Future studies on TGCT should also focus on selecting the most favourable patients and an adequate treatment plan. There is an unmet need to identify patients who will benefit from these drugs, if CSF1R inhibitors applied as (neo)adjuvant therapy improve tumour control and if they are suitable for intermittent usage [41]. Nilotinib seems less appropriate for intermittent use since only 6% achieved partial response and duration of response lasted for 15 months. On the other hand, many patients had ongoing disease control after treatment discontinuation. This suggests that TKI discontinuation in TGCT is not inevitably linked to progression, as seen in other diseases such as advanced gastrointestinal stromal tumours, possibly justifying treatment breaks [42]. Because nilotinib's primary effect in TGCT is considered to target non-neoplastic cells, it is unlikely that treatment breaks promote resistance. Therefore, effective and well-tolerated CSF1R inhibitors could be given for longer durations. We encourage future studies to collect long-term data regarding different treatment durations, retreatment or alternative treatments.

This study contains several limitations. Although the nilotinib phase II study was a prospective trial, current data were retrospectively collected for this long-term study. This resulted in some missing data and follow-up regimes were performed according to local schedules. Secondly, radiological progression, clinical worsening and adverse events were not assessed by validated criteria such as RECIST, patient-reported outcome measurements or CTCAE because this was no longer performed after study completion. Additionally, the criteria such as radiological progression, clinical worsening and tumour operability were assessed by local teams and not centrally. This could possibly introduce assessment bias. However, these criteria were assessed by experts from reference sarcoma centres, which might decrease heterogeneity. Also, all expert centres provided their data and we were able to include all patients from the original study in the current analysis. Finally, since this is a single-arm study, there is an inability to distinguish between treatment effect and natural behaviour of TGCT, which is not well understood to date.

In conclusion, this study reports nilotinib's long-term efficacy. Nilotinib showed mixed long-term efficacy regarding volumetric progression and clinical worsening for patients with advanced D-TGCT. Contrarily, several patients had ongoing disease control after a relatively short treatment duration, which could justify treatment breaks. In addition, no long-term adverse events were observed. However, with the arrival of CSF1R inhibitors showing greater potential, the current role of nilotinib in TGCT is questionable.

Author contributions

Geert Spierenburg: Conceptualization, methodology, investigation, data curation, formal analysis, writing-original draft, writing-review and editing. **Peter Grimison:** Data curation, writing-review and editing. **Christine Chevreau:** Data curation, writing-review and editing. **Silvia Stacchiotti:** Data curation, writing-review and editing. **Sophie Piperno-Neumann:** Data curation, writing-review and editing. **Axel Le Cesne:** Data curation, writing-review and editing. **Virginia Ferraresi:** Data curation, writing-review and editing. **Antoine Italiano:** Data curation, writing-review and editing. **Florence Duffaud:** Data curation, writing-review and editing. **Nicolas Penel:** Data curation, writing-review and editing. **Severine Metzger:** Data curation, writing-review and editing. **Sylvie Chabaud:** Data curation, writing-review and editing. **Lizz van der Heijden:** Conceptualization, writing-original draft, writing-review and editing. **David Pérol:** Data curation, writing-review and editing. **Michiel van de Sande:** Conceptualization, methodology, writing-original draft. writing-review and editing. **Jean Yves-Blay:** Conceptualization, methodology, data curation, writing-review and editing. **Hans Gelderblom:** Conceptualization, methodology, data curation, supervision, writing-original draft, writing-review and editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Grimison, Christine Chevreau, Sophie Piperno-Neumann, Axel Le Cesne, Virginia Ferraresi, Antoine Italiano, Florence Duffaud,

Nicolas Penel, Severine Metzger, Sylvia Chabaud, Lizz van der Heijden, Jean-Yves Blay, Hans Gelderblom declare no conflict of interest within the present study. Silvia Stacchiotti has no conflict of interest to declare within the present study; she reports institutional research funding from Amgen Dompe, Advenchen, Bayer, Blueprint Medicines, Deciphera, Eli Lilly, Epizyme, Daiichi Sankyo Pharma, GSK, Karyopharm, Novartis, Pfizer, PharmaMar, SpringWorks, and Hutchinson MediPharma International Inc; honoraria from Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, and Novartis; invited speaker fees/meeting support from GSK and PharmaMar; fees for expert testimony from Bavarian Nordic and Epizyme; and participation on a Data Safety Monitoring Board or Advisory Board for Bayer, Deciphera, Eli Lilly, Daiichi, Maxivax, and Novartis outside the submitted work. Geert Spierenburg and Michiel van de Sande report institutional research funding from Daichii-Sankyo outside the submitted work. David Perol received personal fees from AstraZeneca, Bayer, Boehringher-Ingelheim, Bristol Myers Squibb, Eli-Lilly, Ipsen, Roche, Novartis, Merck Sharp and Dohme, Takeda.

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Appendix A. Supplementary data

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